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Relationship between pharmacokinetics and pharmacodynamics of β-lactams and outcome

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ABSTRACT

The in-vitro susceptibility of an organism and the pharmacokinetics of an antimicrobial agent are two basic factors on which the choice of standardised treatment regimens is based. However, the inter-individual variability of these factors, which modifies the exposure of bacteria to an antibiotic in terms of time and quantity, is not usually taken into account. In 87 patients treated with β-lactams (ceftriaxone, cefepime or piperacillin), the probability of failure was greater when the infectious process was located in tissues with barriers to the distribution of β-lactams. Mean MICs of piperacillin and cefepime, but not ceftriaxone, were below the breakpoints in cases of both recovery and failure, but organisms isolated from patients with a poor outcome had higher MICs. Therefore, the use of breakpoints to determine the susceptibility of microorganisms was not satisfactory in predicting the outcome for a large number of patients. If MICs are determined and plasma concentrations are monitored, dosages can be adjusted according to these parameters, thereby allowing antibiotic treatment to be individualised.

Keywords β-Lactams, cefepime, ceftriaxone, pharmacodynamics, pharmacokinetics, piperacillin

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INTRODUCTION

In-vitro susceptibility assays often serve as the basis for the choice of antimicrobial therapy, although the correlation between in-vitro and in-vivo results is generally not perfect [1,2]. Once the sensitivity of an infecting organism has been determined, the distribution characteristics of the active antibiotics are evaluated with reference to the location of the infection, and the most suitable antibiotic is chosen after assessment of the patient's clinical condition. The dosage should be decided on the basis of the pharmacokinetics of the antimicrobial agent, as an adequate concentration of the drug must be delivered to the site of infection for antimicrobial therapy to be effective. In most cases, the goal is to obtain plasma and/or tissue concentrations that should at least equal the MIC for the infecting organism.

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Antimicrobial dosages were designed originally to maintain plasma concentrations above the bacterial MIC throughout the dosing interval. Other factors to be considered now include the post-antibiotic effect and the acquisition of resistance [3,4]. Nevertheless, the achievement of therapeutic concentrations of an antimicrobial agent at the site of infection and knowledge of the susceptibility of the infecting organism may not be sufficient to guarantee a cure. Indeed, mortality percentages of 6–33% have been reported for patients in whom the infecting bacteria were susceptible to the treatment administered [3], with rates of clinical or microbiological response of 54–100% [5].

In order to optimise antimicrobial use, certain surrogate markers that define specific relationships between the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of antimicrobials have been used, with very good results, to predict positive patient outcomes [6]. These pharmacokinetic–pharmacodynamic (PK/PD) relationships have become available as tools for individualising antimicrobial therapy, and have led to the

optimisation of dosage regimens to improve the outcome and reduce the selection of resistant mutants. Standardised regimens of β-lactam antibiotics are currently used in the treatment of infectious diseases, despite the fact that it has been established that many of these drugs are eliminated rapidly and that plasma concentrations below the bacterial MIC are observed throughout half of the dosing interval. For bacteria with an MIC near the breakpoint, it is possible that the antibiotic concentration could be below the MIC for almost the entire dosing interval, leading to treatment failure [7]. It is therefore of particular interest to study the relationship between the PK/PD parameters and the efficacy of β-lactam antibiotics. The aim of the present work was to evaluate a PK/PD integration of the ex-vivo PD and in-vivo PK data, with a view to predicting the likely efficacy in clinical use of recommended dose schedules.

MATERIALS AND METHODS

The study, which was conducted over the course of 1 year and approved by the Ethics Committee, included 87 consecutive patients from whom sensitive bacteria were isolated and who were treated by the Infectious Diseases Area, University Hospital of Navarra, with either piperacillin (with or without tazobactam), ceftriaxone or cefepime. Antibiotic selection was on the basis of the microorganism and its antibiogram.

Drugs were administered through a venous catheter in a 30-min infusion after dilution in 100 mL of saline 0.9% v/v. The dose was adjusted to the renal function. Once a steady state was reached (almost five antibiotic half-lives), venous blood samples were taken to determine the plasma concentrations of the antibiotic, before and after the administration of the drug, with two or three samples being taken in the elimination phase. The number of blood samples, and the time at which they were taken, depended on venous accessibility, the clinical situation of the patient, and the patient's consent. The blood was collected from the arm in which drug was not infused. Creatinine clearance was calculated according to the Cockroft–Gault formula [8].

Clinical outcome

Infections were grouped into two categories: those in areas easily accessed by a β-lactam antibiotic, and those in tissues with barriers to distribution (prostate, bone, abscesses). Clinical response was estimated by comparing the symptoms and signs of infection before treatment with those at the end of treatment. The clinical outcome was evaluated as either recovery or failure. Recovery was defined as the partial (improvement) or total (cure) resolution of the symptoms and signs associated with the initial infection, even with persistence of radiological disturbances. Patients were stabilised or showed improvement without the need for prolonged antibiotic treatment after leaving the hospital. Failure was defined as persistence, worsening or reappearance of the symptoms during treatment, or in the week following its termination if initially considered as recovery or improvement. In cases of chronic infection, the patients were under surveillance for almost 6 months.

Data on other active antibiotic treatments or surgery were included as variables that could influence the clinical outcome.

Microbiological data

Biological samples representing the infected area were taken for routine culture. Organisms were isolated from the infectious focus (urine, tracheal secretion, wound secretion or abscesses). For endocarditis, the organism was isolated from blood at different times. For cholecystitis, the same isolate was obtained from bile and blood. MICs were determined with Etests [9]. Only one infecting organism was tested for each patient included in the study; when more than one organism was isolated, the isolate with the higher MIC was chosen.

To facilitate statistical analysis, the isolated bacteria were grouped as follows: (1) Gram-positive cocci; (2) *Pseudomonas aeruginosa*; and (3) a group consisting of the remaining Gram-negative bacilli. Bacteriological response was recorded when it was possible to obtain an appropriate specimen at the end of therapy, or when it was necessary.

Determination of antibiotic concentrations

Total concentrations of the different antibiotics were assayed in the Pharmacokinetic Laboratory, Clinical Pharmacology Service, University Hospital of Navarra. Levels of piperacillin, ceftriaxone and ceftazidime were determined with the use of fully validated high-performance liquid chromatography methods [10–12], with a pump, an autosampler and a UV detector set at 254 nm (Model 1050; Hewlett-Packard, Waldbronn, Germany).

PK data

Different PK parameters were calculated on the basis of plasma concentration and time, using v. 5.1 of the WINNONLIN program (Scientific Consulting Inc., Cary, NC, USA). For the purpose of estimating the parameters, slow-perfusion intravenous administration for 30 min, without lag-time, and first-order elimination from the central compartment was assumed. Three different parameters were calculated: C_{max}, defined as the concentration measured (mg/L) 30 min after the infusion; AUC_{0-t}, defined as the area under the concentration–time curve from 0 to a time t after the administration of the drug (mg × h/L)—the AUC was calculated according to the log trapezoidal rule with almost four values of concentration (13); and C_{min}, defined as the concentration at the end of the administration interval (mg/L).

PK/PD interaction

Different parameters were calculated separately for each patient–treatment–organism combination on the basis of the above data rules, according to the recommendations of Mouton *et al.* [14].

Efficacy time above the MIC (T > MIC) was defined as the time for which the plasma concentrations of the antibiotic were above the MIC for the bacteria. This was calculated between times t_1 and t_2 [6], where t_1 corresponds to the time at which the concentration reaches the MIC during the administration

phase, and t_2 corresponds to the post-infusion time at which the plasma concentration equals the MIC in the elimination phase (Fig. 1). The times were calculated according to the equations

$$t_1 = \frac{MIC - C_{min}}{C_{max} - C_{min}} \times T$$

$$t_2 = \frac{\ln(C_{max}/MIC)}{k}$$

where T is the time of maximum plasma concentration and k is the first-order rate constant of elimination. A percentage calculated over a 24-h period was used in the analysis.

C_{max}/MIC was defined as the ratio between C_{max} and the MIC.

C_{min}/MIC was defined as the ratio between C_{min} and the MIC.

The AUC above MIC, as determined by the trapezoidal rule, was calculated from the plasma concentration minus the MIC at each time interval, over a 24-h period.

The following parameters were also calculated: AUC_{24}/-MIC, defined as the AUC between t_1 and t_2 and the MIC ratio in a dosing interval, multiplied by the number of antibiotic administrations received in 1 day; the free fraction of the antibiotic, calculated from data in the literature, with a view to calculating the efficacy-free time above the MIC (T_{free}/MIC); and the minimum concentration/MIC ($C_{minfree}$/MIC) ratio, with values of 80% for cefepime and piperacillin, and 5% for ceftriaxone) [15–17]. All patients had plasma protein values in the normal range.

Statistical analysis

An initial analysis comprised calculation of the mean, standard deviation and median values. An analysis of the effect of each of the independent or predictable variables on the clinical or microbiological outcome was made with the SPSS program v. 9.0 (SPSS Inc., Chicago, IL, USA), using two techniques of one-by-one forward and backward stepwise introduction of predictive variables into the model. The results were the same with both techniques.

In each analysis, the predictive values that had an influence on recovery were determined. The inclusion of predictive values in the model was based on the log likelihood ratio test; values included were those that were statistically significant if the probability was < 0.05. All of the variables were introduced into the analysis, including treatment duration, surgery and concomitant antibiotics, grouped according to their effect on the infecting microorganisms. A co-variable was considered as a factor of confusion if, when it was withdrawn from the model, the coefficients of the remaining variables varied by $> 15\%$.

An analysis was also done with a chi-square (χ^2) or ANOVA test, depending on whether the variables analysed were qualitative or quantitative, in order to evaluate the differences in a variable depending on whether the effect measured in each analysis was produced. Fisher's Exact Test was used when one or more of the χ^2 groups presented a series of values of < 5. If the samples did not show a normal distribution, or if there was no homogeneity in the variances, parametrical tests were replaced by the corresponding non-parametrical tests (Mann–Whitney *U*-test or Kruskal–Wallis test). Statistical significance was established on the basis of $p < 0.05$.

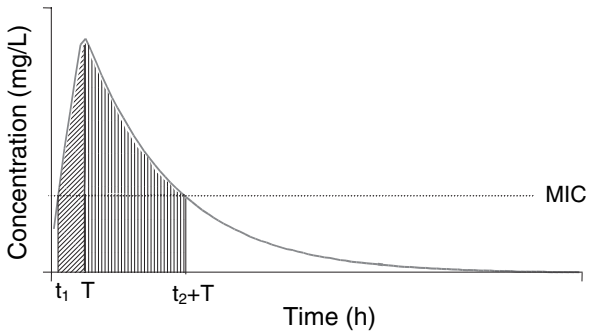

Fig. 1. Illustration of the segments AUC_{t1-T} and $AUC_{T-(t2+T)}$.

RESULTS

Patients

In total, 87 patients (Table 1) were included in this study. Infectious processes, organisms isolated and antibiotic treatment are shown in Tables 2 and 3. The piperacillin–tazobactam combination was used for 49 patients, piperacillin for two patients, cefepime for 13 patients, and ceftriaxone for the remaining 23 patients. In 62.1% of cases, the patient also received another antibiotic. Surgery was performed on 27.6% of the patients, 23% needed intensive care, 33% had a malignant disease, and 9.2% suffered from diabetes mellitus. Among cases of osteomyelitis, 62% were associ-

Table 1. Patient characteristics

	Mean	Range	Median
Age (years)	57.9	21–88	58
Weight (kg)	71.0	50–106	71
Height (cm)	167.8	151–189	168
ClCr (mL/min)	76.9	8–144	85
BMI (kg/m^2)	25.2	16.79–37.18	25

ClCr, creatine clearance; BMI, body mass index.

Table 2. Type of infectious disease, accessibility to antibiotics, and mean treatment duration by the intravenous route

Accessibility	Infection	No. of patients	%	Mean duration (days)
Good	Respiratory	37	42.52	10.6
Poor	Osteomyelitis	9	10.33	10.4
Poor	Prostatitis	2	2.3	20
Poor	Arthritis	4	4.6	32
Poor	Abscess	4	4.6	9
Good	Colecystitis	4	4.6	10
Good	Surgical wound	20	23	16.6
Good	Fistula	6	6.9	16
Poor	Endocarditis	1	1.15	35

Table 3. Organisms identified and antibiotic treatment

Bacterial isolates	No. of bacteria	%	Piperacillin treatment %	Cefepime treatment %	Ceftriaxone treatment %
Staphylococcus spp.	6	6.9	50	–	50
Enterococcus spp.	13	14.9	92.3	–	7.7
Streptococcus spp.	8	9.2	50	–	50
Enterobacteriaceae	26	29.9	50	19.2	30.8
Haemophilus influenzae	6	6.9	–	–	100
Pseudomonas aeruginosa	24	27.6	66.7	33.3	–
Corynebacterium spp.	1	1.15	100	–	–
Anaerobes	3	3.45	100	–	–

ated with a foreign body, which was removed from two-thirds of these patients. Patients with osteomyelitis required oral antibiotic therapy (mean duration 5 months) before leaving the hospital. Endocarditis was treated for 35 days.

An analysis of the clinical outcome was possible for all cases. In total, 65 (74.7%) patients recovered, corresponding to 68.6% of those who received treatment with piperacillin (± tazobactam), 84.6% of those treated with cefepime, and 82.6% of those who received ceftriaxone. Treatment failed in 22 patients.

Analysis according to treatment group

Patients treated with piperacillin

This group of patients included 37 males and 14 females aged 21–88 years, of whom 81.6% had creatinine clearance values >40 mL/min. These patients were treated with piperacillin, in most cases in combination with tazobactam.

The organisms isolated from this group had a mean MIC of 5.79 mg/L (standard deviation 5.92 mg/L). Most (40) patients received 4 g of piperacillin with 0.5 g of tazobactam every 8 h. Of the patients with respiratory infection, 83.3% had an adequate clinical outcome, compared to 76.5% of patients with infections in other locations easily accessed by this drug, and to only 25% of patients where there were barriers.

The mean values of the PK/PD parameters obtained from this group of patients are shown in Table 4. The mean maximum concentration value (156.7 mg/L) in the patients who received 4 g of piperacillin was double that obtained through the administration of 2 g (78.5 mg/L). In 14 patients, piperacillin was not detected in the blood sample obtained pre-dose. The plasma clearance of piperacillin was directly proportional to plasma creatinine clearance, whereas its half-life elimination was shorter when the clearance was higher.

Among the 51 patients treated with piperacillin, the infectious process improved or was resolved after antibiotic treatment in 35. Statistically significant differences were observed between both groups in terms of the MIC for the isolated bacteria (p 0.026), the type of infection ($p < 0.001$), and whether or not there was surgery (p 0.044). When clinical outcome was inadequate, either MIC values were higher, infection was located in tissues with barriers, or some kind of surgery was required. All of the PK/PD variables were different, depending on the outcome. A gradient in the value of variables was observed if they were analysed on the basis of the three possible clinical outcomes, as shown in Table 5 and Fig. 2. The highest value was associated with resolution of the infectious process.

Table 4. Pharmacokinetic and pharmacokinetic/pharmacodynamic parameters

	Piperacillin		Cefepime		Ceftriaxone	
Parameter	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**
Dose/administration (mg)	3843 ± 543	4000	1615.4 ± 869.7	1000	1956.5 ± 208.5	2000
Interval (h)	8 ± 2.7	8	12.2 ± 6.95	8	24	24
Total clearance (L/h)	12.8 ± 6.96	11.3	5 ± 3.1	5.8	1.4 ± 0.65	1.3
AUC_{0-t} (mg × h/L)	400.5 ± 220.9	343.4	354.99 ± 205.1	260.93	1421.2 ± 674.6	1269.4
AUC_{0-24} (mg × h/L)	1175.1 ± 567.6	1003	736.4 ± 272.8	757.4	1421.2 ± 674.6	1269.4
Peak concentration (mg/L)	159.59 ± 50.21	155.59	69.86 ± 22.35	69.11	134.64 ± 51.89	120.4
Total trough concentration (mg/L)	9.71 ± 14.26	4.59	16.10 ± 11.73	15.35	22.77 ± 16.29	19.78
Unbound trough concentration (mg/L)	7.3 ± 10.68	3.44	12.85 ± 9.23	12.28	1.14 ± 0.8	0.99
% $T >$ MIC	86.4 ± 18.9	98	97.3 ± 35.4	100	95.8 ± 13.74	100
% $T_{free} >$ MIC	83.2 ± 20.4	84.6	95.3 ± 8.9	100	84.2 ± 32.2	100
AUC above MIC (mg × h/L)	1066.33 ± 571.3	935.6	625 ± 256.5	662.4	1330.5 ± 743.3	1173.4
AUC_{24}/MIC (h)	1168.8 ± 3310.9	234.6	2940.5 ± 6627.3	173.6	19186.9 ± 30894	3559.9
C_{max}/MIC	159.9 ± 421.4	39.58	229.7 ± 508.4	15.7	1796.1 ± 2833.9	286.2
C_{min}/MIC	11.5 ± 53.7	0.78	75.8 ± 182.7	2.53	307.1 ± 543.4	61.7
$C_{min\ free}$/MIC	8.9 ± 41	0.57	60.6 ± 146	2.03	61.4 ± 109	12.3

For abbreviations, see main text.

Patients treated with cefepime

Of the patients treated with cefepime (14.9%; $n = 13$), four had severe renal dysfunction. The mean MIC for the microorganisms identified was 4.73 ± 4.25 mg/L. The clinical outcome was adequate in 84.6% of these patients, and no relapses occurred. Of the organisms isolated, 40% of *Pseudomonas aeruginosa* isolates were eliminated, as were 75% of the remaining Gram-negative bacilli. The mean PK/PD parameters calculated for this group of patients are shown in Table 4. The clinical outcome was satisfactory in 11 patients who received treatment with cefepime, and no statistically significant differences between the two groups were observed in the non-parametric studies applied. Although there was an apparently poorer outcome if *P. aeruginosa* was isolated, this was either because the infection was located in tissues with barriers, the patients were older, or the patients were treated with cefepime monotherapy. Non-parametric tests revealed statistically significant differences in the efficacy time above the MIC of both the free and total fractions of cefepime. No differences were detected in other parameters, but the trend described above for piperacillin could be detected (Table 5).

Patients treated with ceftriaxone

Twenty-three (26.4%) patients were treated with ceftriaxone. The mean MIC for the bacteria isolated from this group of patients was 4.3 mg/L (standard deviation 9.11 mg/L; median 0.5 mg/L).One strain of *Enterobacter cloacae* had an MIC of 32 mg/L. The dose and PK/PD parameters for this group of patients are shown in Table 4.

The clinical outcome was favourable for 19 patients treated with ceftriaxone, and statistically significant differences in the MICs for the isolated bacteria were observed between these 19 patients and the remaining four patients (p 0.03). The duration of treatment also differed, being shorter in those patients with a poorer outcome (p 0.045). The PK/PD parameters also showed significant differences, with values that gradually declined as the clinical outcome deteriorated (Table 5). For ceftriaxone, the magnitude of some of these parameters was considerable even when the outcome was inadequate. In terms of free drug concentration, given that a high proportion of ceftriaxone is protein-bound, this value was similar to that observed with the other drugs studied, and was lower in patients with an inadequate clinical outcome.

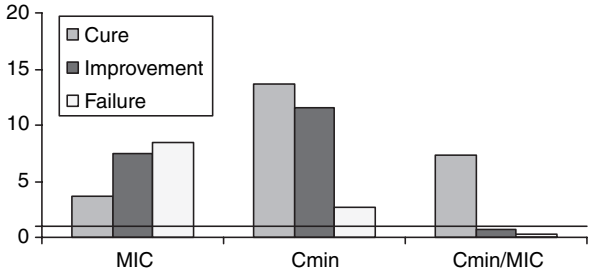

Fig. 2. MIC, trough concentration and ratio in relation to clinical outcome (the horizontal line represents the unit value).

Multivariate analysis

Table 6 shows the differences between PK/PD parameters in relation to outcome. A multivariate analysis was done, with favourable clinical outcome as the reference category. The probability of an inadequate clinical outcome increased with the presence of *P. aeruginosa* (p 0.039) and

Table 5. Pharmacokinetic/pharmacodynamic parameters (mean values) related to treatment and clinical outcome

	MIC	C_{min}	C_{min}/MIC	AUC above MIC	AUC_{24}/MIC	C_{max}/MIC	$C_{min\ free}$	$C_{min\ free}$/MIC
Piperacillin								
Cure	3.67	13.7	7.32	1182.58	1343.96	209.85	10.3	5.49
Improvement	7.44	11.6	0.72	1463.45	232.66	28.35	8.7	0.54
Failure	8.47	2.7	0.27	718.20	156.75	30.12	2.2	0.2
p	0.021	0.008	< 0.001	0.002	< 0.001	0.009	0.008	< 0.001
Cefepime								
Cure	3.14	18.2	15.2	709.35	4450.37	55.21	14.2	12.2
Improvement	5.58	18.3	2.54	608.21	2877.94	12.14	12.4	2.03
Failure	5.00	3.7	0.77	515.40	139.47	19.65	3	0.62
Ceftriaxone								
Cure	1.15	22.8	451	1456.91	26524.25	2297.72	1.2	22.6
Improvement	0.87	27	199.1	1515.18	16017.37	1899.29	1.4	9.9
Failure	19.50	16.3	1.69	642.74	94.96	10.86	0.8	0.08

For abbreviations, see main text.

the existence of barriers in the infected tissue (p 0.005), while high values of efficacy time above the MIC (p 0.002), AUC above MIC (p 0.04), and higher age (p 0.039) reduced this probability (Table 7). The surgery variable acted as a factor of confusion, so it was retained in the model despite the fact that its influence as a predictive factor of clinical outcome was not significant.

DISCUSSION

The use of microbiological parameters that provide information about the susceptibility of an infecting pathogen is the traditional approach to the clinical treatment of infectious disease. These PD parameters are used to establish the optimal antimicrobial agent for treatment. PK data give information about the potential ability of a drug to reach and remain at the sites of infection, and are used to determine the dose and the dosing interval. In clinical practice, PK parameters derived from the general population are usually employed in order to establish the dose. However, this is not a patient-specific approach; from the perspective of optimisation of outcome in everyday clinical practice, the best scenario would be the employment of PK parameters obtained directly from the individual patient.

The mean PK parameters observed in the three groups of patients studied were similar to those described in the general population, if renal function was considered [18]. However, high variability in the values of the PK parameters was observed, with clearance values of > 50% in many cases. Moreover, undetectable concentrations at the end of the dosing interval were observed in certain patients, especially after doses of piperacillin.

With regard to the mean bacterial MICs for the groups of patients studied, it was interesting to note that this parameter was below the breakpoint for each antibiotic in cases of recovery and failure for patients treated with piperacillin (± tazobactam) or cefepime. In the case of ceftriaxone, MICs above the breakpoint were found exclusively for patients with an inadequate outcome. These results suggest that susceptibility breakpoints were not satisfactory for a large number of patients, as has been stated elsewhere [19]. In the present study, the patients with an unfavourable outcome should have had a good response with piperacillin or cefepime, based on the antibiogram. It has been reported elsewhere that, despite the fact that the bacteria analysed are apparently susceptible to treatment, patients with an inadequate outcome have infecting bacteria with higher MIC values compared to patients who recover [3].

Based on these observations, it is necessary to investigate other methods to improve the prognosis for this group of patients. The present study demonstrated that the integration of PK and microbiological parameters might be of use in the design of therapeutic regimens for β-lactams. Thus, the time for which the concentration of piperacillin exceeds the MIC ($T >$ MIC or efficacy time) is commonly considered to represent the relevant surrogate parameter for evaluating antimicrobial activity and therapeutic success. In the group of patients who had a favourable outcome, the time for which the concentration of piperacillin exceeded the MIC was 97% of the dosing interval, whereas a value of 71.5% was obtained in patients whose outcome was inadequate. Therefore, a value of 90% was defined for this parameter, to differentiate between potential recovery and failure. Traditionally, it has been considered that $T >$ MIC for Gram-negative bacilli or streptococci should be equal to the dosing interval [20,21], but the results of recent studies have shown that it is sufficient for the concentration to be above the MIC for 60–70% of

Table 6. Pharmacokinetic/pharmacodynamic parameters depending on clinical outcome

	Recovery	Failure
% time above MIC	97 ± 8.9	71.5 ± 20.5
% time above MIC (unbound)	94.5 ± 11.7	58.1 ± 27
AUC above MIC (mg × h/L)	1209.7 ± 646.2	658.2 ± 282.8
AUC_{24}/MIC (h)	8246.2 ± 20272	142.4 ± 99.7
C_{max}/MIC	798.1 ± 1870	26.2 ± 21.6
C_{min}/MIC	132.7 ± 356.8	0.5 ± 0.9

Table 7. Multivariate analysis of the influence of predictor variables on antimicrobial treatment failure

	B	Standard error	p Likelihood ratio test
Efficacy time above MIC	− 0.11	0.04	0.002
Pseudomonas			
No	1 (ref.)		
Yes	1.97	0.96	0.039
Age	0.07	0.04	0.040
Infection			
Without barriers	1 (ref.)		
With barriers	2.87	1.02	0.005
AUC above MIC	− 0.003	0.001	0.040

the dosing interval for penicillins and cephalosporins [3,22], with 50% being the value for Gram-positive cocci [23]. The present data are closer to the first figure, given that the outcome was unfavourable with a mean efficacy time above the MIC of 71.5% of the dosing interval. In addition, a new PK/PD index was identified that is predictive of the clinical antimicrobial effect, namely the AUC above MIC. To date, this parameter has not been considered as a predictor of efficacy, although Schentag *et al.* [6,24,25] considered this index to be the best tool for adjusting the dosage of any antibiotic. However, its use has detractors [26], because different plasma concentration profiles can result in the same AUC values, despite the fact that the time for which the plasma concentration is higher than the MIC may be quite different.

The results obtained in the present study confirmed the need to maintain concentrations above the MIC for a length period. Thus, the clinical outcome in the patients depended on the time for which the concentration of piperacillin exceeded the MIC along the dosing interval, and the AUC above MIC. For antibiotics that are predominantly eliminated by the kidneys, the plasma concentrations of drug are increased proportionally with the dose. Similar results can be obtained by reducing the dosing interval. Therefore, the best way to increase the probability of a good clinical outcome is to increase the dose or to reduce the dosing interval. Once the maximum efficacy time above the MIC has been achieved, the prognosis can be improved further by increasing the AUC above MIC. This becomes particularly important in the treatment of infectious processes located at sites that β-lactams have difficulty accessing, or for infections caused by *P. aeruginosa*. This index is also a better predictor than the efficacy time above the MIC, because it does not have a maximum value [27].

In the present study, the clinical outcome of the infections analysed also depended on their location, so the probability of an inadequate outcome was greater if they were found in tissues that are difficult to access, such as in the case of prostate or bone infections, or purulent collections. The difficulty that many drugs have in accessing these locations has been described extensively [7,28,29]. Therefore, higher AUC above MIC values and maximum efficacy time above the MIC values in plasma are required to reduce the probability of treatment failure in these patients [30]. However, in easily accessed tissues, the efficacy time and the plasma AUC above the MIC can constitute a accurate reflection of what occurs at the tissue level. In tissues where the β-lactam concentration is high (above that of plasma), the outcome of an infectious process is more likely to be favourable, since both the efficacy time and the AUC above the MIC in the plasma underestimate the situation in these tissues. This would be the case for urine or bile [31,32].

Age was also considered to be a predictive factor of outcome, which was better at a greater age. Elderly patients show diminished elimination rates, including a reduction in renal clearance. Therefore, drugs remain for longer periods of time and at higher concentrations. Consequently, the efficacy time above the MIC is higher in the elderly [33].

Another determining factor of the clinical outcome was the type of organism isolated; thus the prognosis was clearly worse when *P. aeruginosa* was identified as the infecting organism. The results obtained in the present study were similar to those reported previously [6,34]. On the other hand, there was no difference in outcome depending on other variables, such as concomitant antibiotics or surgery, probably because their incidence was similar in both groups.

The analysis of the clinical outcome demonstrated that the values of all the PK/PD variables studied were lower when treatment failed. The data appear to support the concept that it is necessary to maintain the plasma concentration of a β-lactam at 4–8-fold the MIC to achieve efficacy [35,36]. This conclusion has also been reached in animal and in-vitro studies [37–39], and was supported by findings in patients where an infection produced by *P. aeruginosa* was detected, with a mean C_{min}/MIC value of 3.56 in patients who recovered, compared with 0.28 when the treatment failed. The case of ceftriaxone is different because the values were much higher, mainly because the MIC values were much lower and the plasma concentrations higher. Nevertheless, the ratio calculated in terms of the fraction of unbound drug was similar to that found for the other two drugs, with values lower than one unit in the patients with an inadequate outcome. The low number of patients in some groups did not allow statistical comparisons, although the trend was similar.

These observations confirm that determination of the plasma concentration in each patient is also useful for individualising the dosage of β-lactams, and thus obtaining therapeutic plasma concentrations. The development of PK/PD parameters that overcome the requirement to determine plasma concentrations on a day-to-day basis to tailor the PK system for individual patients may be more likely to achieve the desired antimicrobial concentration–response relationship and enable the optimum patient–dosage regimen to be established.

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